REMARKS

In the Official Action of September 22, 2004, the pending claims were subject to restriction under 37 CFR 1.142(b) stating that claims 52-54, drawn to a method for preparing a colloidal composition, are independent and distinct from claim 6-13, 15-16, 18, 20-12, 30-32 and 50-51, drawn to a liquid composition. The Examiner states that applicant has constructively elected the composition claims as a result of the original presentation of these claims in the prior application. Consequently, claims 52-54 have now been withdrawn from prosecution, and claim 30-32 have been canceled.

Claims 6, 10-13, 16, 18, 20-21, 30-32 and 50-51 have been rejected under 35 U.S.C. 103(a) as being obvious over Van Ness et al. (U.S. Patent No. 5,667,976), in view of Grieve et al. (U.S. Patent No. 6,391,569) and Malvar et al. (U.S. Patent No. 6,110,464). This ground of rejection is traversed.

The claims have now been amended to include at least one reference dye in the liquid composition. Antecedent support for this amendment is found on pages 15 and 16 of the present specification. As stated in the specification, the reference dye can serve as a marker for determining the quantity of biomolecule deposited in a specific spot on a microarray, as may be useful for manufacturing quality control and/or as an internal reference standard for quantifying the optical signal of the labeled biomolecule. The reference dye can also be used to track the concentration of matrix material during the preparation of the liquid composition. None of the references cited in the Office Action disclose the use of reference dyes for quality control or manufacturing purposes.

The Van Ness et al. reference relates to solid supports for nucleic hybridization assays using polymer nylon coated magnetic beads. Oligonucleotides are attached to the beads by covalent bonding to form nucleotide probes. The nylon coated beads of Van Ness et al. have dimensions of from about 0.01 inches to 0.5 inches in diameter. See col. 3, lines 48-62 of the reference. The Examiner recognizes that the Van Ness et al. reference does not disclose proteins.

The Grieve et al. reference has been cited as teaching the immobilization of a protein on a solid support, such as nylon, nitrocellulose or PDF. Both particulate and non-particulate (plates) substrates are disclosed in the reference.

The Malvar et al. reference discloses the immobilization of proteins or peptides onto the well of a polystyrene microtiter plate in order to perform an ELISA assay. The well is treated with a non-specific binding protein in order to filter out unwanted background noise.

The Examiner contends that it would be obvious to combine these references in order to arrive at the present invention The Examiner further contends that the selection of the particular size of particles claimed in the present invention is not a patentable feature and is in fact an obvious matter of design choice, citing *In re Rose*, 105 USPQ 237 (CCPA 1955).

It is applicant's position that the *Rose* case stands for the proposition that incremental changes in the size of an article is ordinarily not a matter of invention. Specifically, in the *Rose* case, the articles under consideration by the Court were lumber strips which were marginally larger than the lumber strips used in the prior art. This was held to be a difference in degree rather than a difference in kind. However, the Patent Office has long recognized that a difference in degree can be substantial enough to amount to a difference in kind. See, for instance, *In re Shepard*, 138 USPQ 148 (CCPA 1963), which specifically relates to the patentability of particles based on differences in particle sizing.

In the instant application, the claimed particles are colloidal particles formed by dispersing the particles in a liquid medium as a suspension. The colloidal particles of this invention are less than about 1 micron (0.000001 meters, or about 0.00004 inches) in diameter. This compares with the particles of Van Ness et al. which are at least 0.01 inches in diameter. Thus, the particles of the reference are more than 2 orders of magnitude larger than the particles of the present invention. Applicant submits that this is a difference in kind rather than a mere difference in degree. Note, for instance, that the reference fails to teach or suggest how one skilled in the art would prepare suitable particles of the size claimed in the present application, or how the technology which could be used by one skilled in the art to attach oligonucleotides or proteins to such microparticles.

Applicant again points out that the substantially reduced size of the microparticles of this invention produce enhanced results compared to the larger particles used in the prior art. See Example V of the present invention, which illustrates an enhancement in sensitivity, and Example VI, illustrating the reduction in nitrocellulose levels and the associated background fluorescence, as compared to the prior art. These results are beyond the mere incremental improvements which could be predicted by routine design choices.

Applicant has also carefully reviewed the Malvar et al. reference. The Examiner states that Malvar et al. describes the coating of a surface with a non-specific protein, such as BSA, to block background noise. However, the surfaces blocked in the Malvar et al. reference are the surfaces of a microtiter well, not the surfaces of particles to which probes are bound.

Finally, the combination of references cited in the Office Action fails to disclose liquid compositions containing a reference dye which can be used for quality control or manufacturing assurance purposes.

Claims 6-13, 16, 20-21, 30-32 and 50-51 stand rejected under 35 U.S.C. 103(a) as obvious over Nagai et al. (U.S. Patent No. 5,667,976), in view of Grieve et al. and Malvar et al.

The Nagai et al. reference discloses methods for detecting genomic disorders through the use of labeled single-stranded nucleic acid probes bound to fine particles in solution. The probes are complementary to first and second regions of the target genomic molecule. The particles of Nagai et al. are defined as polystryrene beads having a diameter of 300 nm. See col. 8, lines 41-60 of the reference. The Examiner acknowledges that Nagai et al. does not disclose the immobilization of proteins, but contends that the Grieve et al. reference cures this problem.

There is no disclosure in the Nagai et al. reference that a uniform colloidal suspension of particles is formed as required in the present claims. In fact, the reference states that the particles aggregate in solution, and this would not be the case for a colloidal suspension. See col. 8, lines 16-25 of the reference. Moreover, the use of a dye as claimed in the present application is not taught or suggested in Nagai, et al.

Claims 6-13, 15-16, 18, 20-21, 30-32 and 50-51 have also been rejected under 35 U.S.C. 103(a) as obvious over Delair et al. (U.S. Patent No. 6,033,853), in view of Grieve et al. and Malvar et al. This ground of rejection is respectfully traversed.

Delair et al. describes kits for detecting specific target nucleic acid sequences using labeled probes. The kits include a suspension of insoluble particles bound to identical oligonucleotides. The latex particles in the suspension have size ranges of from 50 nm to 5 μm. In addition, the latex of Delair et al. is prepared from a vinyl monomer, such as styrene, rather than from nitrocellulose, activated nylon, or polyvinyl difluoride, as required in the present claims.

Although the Examiner argues that the it would have been obvious to use the polymers of Grieve et al. (nitrocellulose, PVDF or nylon) in place of the styrene latex of Delair et al., no

reason has been advanced as to why one skilled in the art would be led to make this substitution. Moreover, there is no disclosure in either reference regarding the preparation of suspensions of nitrocellulose, PVDF or nylon, or how such suspensions could be used to affix a biomolecule to the microparticles contained in such suspensions.

Even assuming that the Delair et al., Grieve et al., and Malvar et al. references are properly combinable, the result of such a combination would still fail to teach or suggest the use of at least one reference dye in a liquid suspension containing a biomolecule of interest for quality control purposes, as an internal reference standard, or for manufacturing control as claimed in the present claims.

Claims 6, 10-13, 16, 20-21, 30-32 and 50-51 stand rejected under 35 U.S.C. 103(a) as obvious over Kawaguchi et al. (U.S. Patent No. 5,122,600) in view of Grieve et al. and Malvar et al. This ground of rejection is traversed.

Kawaguchi et al. discloses DNA-immobilized microspheres for the specific binding of proteins, and a carrier having a particle size of from about 0.01 μm to 50 μm. The carrier particles of the reference are formed from hydrophilic polymers selected on the basis of their ability to absorb proteins. Col. 3, lines 25-56. The polymers of the reference are basically acrylic polymers and copolymers, and do not include nitrocellulose, polyvinyl difluoride or activated nylon.

In addition, and as mentioned above in connection with other references, there is no disclosure in Kawaguchi et al. regarding the use of a reference dye in a liquid suspension for the purposes mentioned above.

The Grieve et al. reference is not deemed to correct the deficiencies of the Kawaguchi et al . reference as discussed herein.

Claims 6-13, 15-16, 18, 20-21, 30-32 and 50-51 have been rejected under 35 U.S.C. 103(a) as obvious over Seul (WO 97/40385) in view of Malvar et al. This ground of rejection is also traversed.

The Examiner states that the Seul reference teaches the manipulation of colloidal particles ranging in size from 1 to 10 microns. The particles can include a plurality of molecules, which can be oligonucleotides or proteins, and the colloid can also include labeling agents.

Applicant points out that the instant claims embrace particles having an average size of less than the 1 to 10 micron particle size range recited in the Seul reference. In addition, Seul

does not teach or suggest the use of reference dyes for the purposes described and claimed in the present application.

Summarizing, applicants do not agree that the particle size differences are strictly matters of design choice as contended by the Examiner where the reference relied upon contains no disclosure regarding the technology required for reducing the particle size to meet the claimed range. In this respect, the references relied upon are viewed as enabling. Moreover, no motivation has been supplied for making the suggested modifications, and no reasonable expectation for success has been provided. Finally, the references are silent regarding the use of reference dyes as claimed in the present invention.

In view of the foregoing facts and reasons, this application is now believed to overcome the remaining rejections, and to be in proper condition for allowance. Accordingly, reconsideration and withdrawal of the rejections, and favorable action on this application, is solicited. The Examiner is invited to contact the undersigned at the telephone number listed below to discuss the status of this application.

Respectfully submitted,

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